Case Report

Annals of Clinical and Medical Case Reports

# Central Neurogenic Hyperventilation as a Manifestation of BRAF V600E– Mutated Erdheim–Chester Disease with Isolated Central Nervous System Involvement: A Case Report

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**Received Date:** 31 Mar 2026
**Accepted Date:** 10 Apr 2026
**Published Date:** 17 Apr 2026

**Citation:** Vazquez Cerro, Rocio, Central Neurogenic Hyperventilation as a Manifestation of BRAF V600E– Mutated Erdheim–Chester Disease with Isolated Central Nervous System Involvement: A Case Report. Annals of Clinical and Medical Case Reports 2026; 15: 1-4

## 1. Abstract

**1.1. Background:** Erdheim–Chester disease (ECD) is a rare non-Langerhans cell histiocytosis frequently associated with activating MAPK pathway mutations, most commonly BRAF V600E. Central nervous system (CNS) involvement is present in a substantial subset of patients but isolated CNS presentations are uncommon. Central neurogenic hyperventilation (CNH) is a rare respiratory disorder associated with lesions of central respiratory control and has been rarely reported in ECD.

**1.2. Case Presentation:** A 38-year-old man developed progressive dysarthria, left upper-limb ataxia and bilateral lower-limb weakness. Brain and spine MRI showed multifocal infiltrative lesions involving the brainstem, cerebellum, thalamus and spinal cord with homogeneous contrast enhancement and mass effect on the fourth ventricle and prepontine cistern. CSF analysis and extensive systemic workup were non-diagnostic. An initial open biopsy of a cerebellar peduncle was nondiagnostic. Due to clinical and radiological progression, a second biopsy of the brainstem–cerebellar lesion established the diagnosis of non-Langerhans cell histiocytosis consistent with Erdheim–Chester disease, with immunohistochemical detection of BRAF V600E.

Immediately after the second neurosurgical procedure, the patient developed persistent tachypnea, respiratory alkalosis and hyperlactatemia without hypoxemia or hemodynamic instability. Propofol infusion syndrome was considered (elevated CPK), but triglycerides and methemoglobin were normal; ketonuria and procalcitonin were negative. After exhaustive exclusion of infectious, metabolic and toxic etiologies, CNH was diagnosed.

The patient started on vemurafenib 960 mg twice daily. At follow-up, an 18F-FDG cravinale@fleni.org.ar PET-CT performed on 21 November 2025 (compared with a PET-CT from 25 October 2024) demonstrated resolution of previously described hypermetabolic brain lesions and a reduction in spinal cord metabolic activity. Clinically, the patient tolerated full-dose vemurafenib, with increased cutaneous photosensitivity and mild plantar desquamation; adherence was intermittently affected by delays in medication delivery due to the patient's health coverage. Functionally, he reports fluctuating neurological deficits, limited mobility (walks no more than half a block), reduced engagement with physiotherapy (one session/week) and no ongoing psychotherapy. Supportive medications included quetiapine 12.5 mg for insomnia.

**1.3. Conclusion:** This case documents CNH as a rare but important complication of CNS-limited BRAF V600E–mutated ECD and demonstrates objective metabolic response to BRAF inhibition. The report underscores the need for early molecular testing in infiltrative CNS histiocytosis. It highlights that radiological/metabolic response may precede or partially dissociate from functional recovery, emphasising the role of sustained multidisciplinary supportive care.

**2. Keywords:** Erdheim–Chester disease; central neurogenic hyperventilation; BRAF V600E; vemurafenib; brainstem; case report

## 3. Introduction

Erdheim–Chester disease (ECD) is a rare multisystem histiocytosis defined pathologically by tissue infiltration with CD68-positive, CD1a-negative foamy histiocytesm [1]. Activating mutations in the MAPK signalling pathway—most notably BRAF V600E—are found in a substantial proportion of cases and have transformed therapeutic options by enabling targeted therapy with BRAF and MEK inhibitors [1, 2]. CNS involvement occurs in approximately 25–50% of patients and commonly affects the posterior fossa and brainstem1; isolated CNS-limited disease is less frequent and can be diagnostically challenging [1].

Central neurogenic hyperventilation (CNH) is characterised by sustained hyperventilation not explained by systemic hypoxia, metabolic acidosis, pulmonary disease or psychogenic causes [3],

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and is classically associated with lesions of brainstem respiratory centres and adjacent diencephalic structures [4]. CNH has been described infrequently in association with primary CNS tumours, inflammatory lesions, and brainstem metastases [4-6]; reports linking CNH to ECD are exceedingly rare [2]. We present a case of isolated CNS ECD harbouring BRAF V600E that was complicated post-operatively by CNH [7] and subsequently demonstrated metabolic response to vemurafenib [1,2].

## 4. Case Presentation

A 38-year-old man with no significant previous neurological history presented with progressive dysarthria, imbalance and left upper-limb incoordination over several months, accompanied by insidious bilateral lower-limb weakness. Neurological examination revealed cerebellar dysarthria, left brachial ataxia and spastic paraparesis.

## 5. Investigations

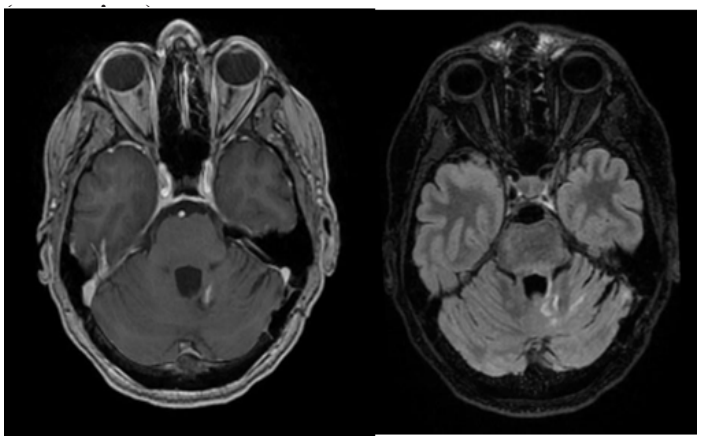
Brain and spinal MRI demonstrated multiple hyperintense lesions on T2 and FLAIR sequences affecting the right thalamus and internal capsule, the splenium of the corpus callosum, bilateral centrum semiovale, extensive involvement of the brainstem and both cerebellar hemispheres (with associated swelling and intense contrast enhancement),

and multifocal spinal cord lesions, some of which enhanced. There was mass effect on the fourth ventricle and loss of normal prepontine cistern anatomy.

Lumbar puncture showed opening pressure 11 cm$H_2O$; CSF contained 2 leukocytes/$mm^3$, protein 118 mg/dL, glucose 57 mg/dL (serum glucose 85 mg/dL) and lactate 1.5 mmol/L. Cytology, bacterial and fungal cultures, and flow cytometry were unremarkable. Serum anti-ganglioside antibodies (IgM, IgG) were negative.

Extensive systemic workup-including whole-body contrast CT, digital subtraction angiography, transthoracic echocardiography, renal ultrasound and bone scintigraphy-failed to reveal extracranial disease.

Figure 1: **Admission MRI** (T2/FLAIR and Ti+C) and control



**05/03/2024** MRI T1 Cube Fat Sat – T2 FLAIR Cube

An 18F-FDG PET-CT (25 October 2024) identified hypermetabolic foci in the right basal ganglia, left middle cerebellar peduncle, left cerebellum (SUVmax 16.8) and brainstem. Given the presumptive inflammatory/autoimmune differential diagnosis, the patient received high-dose intravenous methylprednisolone (total 5 g) and five sessions of plasmapheresis without clinical benefit. He was discharged but readmitted four months later with neurological progression. A first open biopsy of a cerebellar peduncle lesion was nondiagnostic.

Because of continued progression, a second open biopsy sampling of the diffuse brainstem–cerebellar lesion was performed. Histopathology showed a histiocytic infiltrate with foamy CD 68-positive, CD 1a-negative cells consistent with non- Langerhans cell histiocytosis (ECD). Immunohistochemical testing detected BRAF V600E.

## 6. Perioperative respiratory event and diagnosis of CNH

In the immediate postoperative period, the patient developed persistent tachypnoea and hyperpnoea. However, he remained well oxygenated without supplemental oxygen and maintained stable haemodynamics. Arterial blood gases showed respiratory alkalosis in association with metabolic acidosis and elevated lactate. Propofol infusion syndrome (PRIS) was considered, given intraoperative propofol exposure; CPK was elevated, but serum triglycerides and methemoglobin were normal. Ketonuria and procalcitonin were negative; infectious, metabolic and toxic causes were excluded. The clinical picture-sustained hyperventilation unexplained by extracerebral triggers and in the context of brainstem infiltration was interpreted as central neurogenic hyperventilation (CNH).

## 7. Treatment and Follow-up

Following molecular confirmation of BRAF V600E, the patient was started on vemurafenib 960 mg twice daily. Management and follow-up were conducted largely via teleconsultation because of geographic and logistical constraints. Supportive medications included quetiapine 12.5 mg nightly for insomnia.

At outpatient follow-up, the patient reported tolerating full-dose vemurafenib with manageable adverse effects primarily increased cutaneous photosensitivity and mild plantar desquamation. He had not attended dermatology for follow-up despite recommendations. Adherence was intermittently compromised by delays in medication provision related to the patient's insurance/coverage. The patient's engagement with rehabilitation was limited; reports indicated they attended physiotherapy one day per week only, and sessions were often suspended. They were not undergoing ongoing psychotherapy.

A family member reported a fluctuating clinical status. Functionally, the patient remained limited: he reported an inability to walk more than half a block and experienced fatigue easily when exposed to heat.

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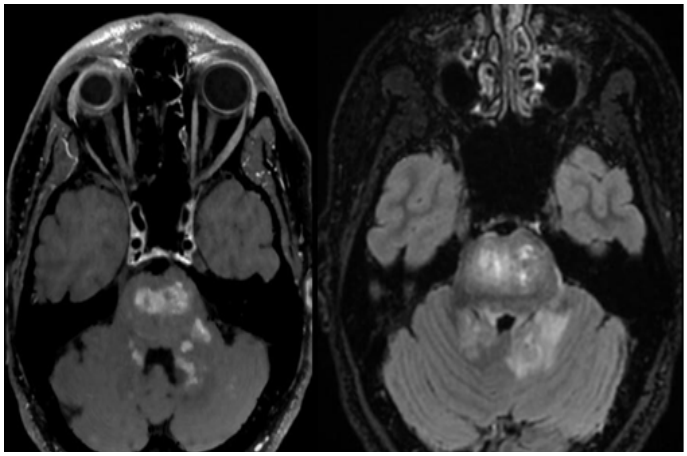
Figure 2 - **Baseline PET FDG** and control **(comparison)**



**03/01/2025** MRI AXIAL T1 Cube Fat Sat – T2 FLAIR Cube

A control 18F-FDG PET-CT performed on 21 November 2025 (following the baseline PET-CT from 25 October 2024) demonstrated resolution of the previously described hypermetabolic foci in the cerebellar peduncle, cerebellum and brainstem. Spinal cord involvement persisted, but with decreased metabolic activity—the area of greatest uptake moved to D11–D12 with SUVmax 3.0 (prior SUVmax 3.9). No new abnormal tracer uptake was identified. Incidental tomographic findings included posterior fossa surgical sequelae and mild multilevel spondylosis.
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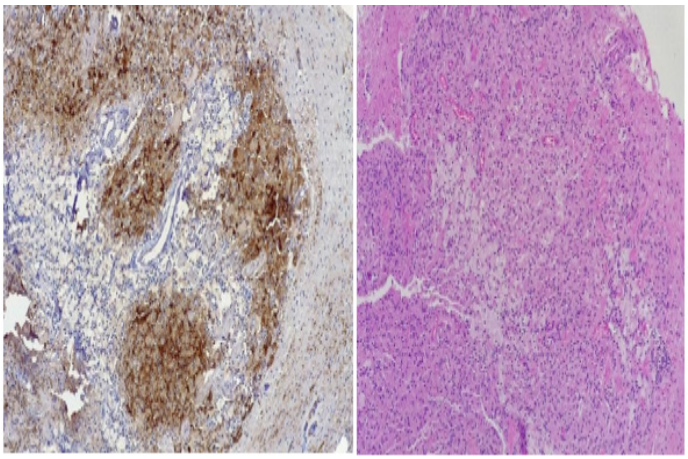
Figure 3: **Histology + BRAF V600E** immunohistochemistry



Histological Sections in Hematoxylin-eosin + BRAF V 600e staining

## 8. Discussion

This case provides an instructive example of several clinically important and biologically plausible observations in CNS ECD.

**1) Diagnostic challenge of CNS-limited ECD**

The initial clinical and radiological presentation—multifocal infiltrative supratentorial and infratentorial lesions with spinal cord involvement—mimicked inflammatory processes: CSF was non-diagnostic, and the first biopsy was non-diagnostic, underscoring how tissue sampling site and sampling adequacy are critical in infiltrative brain lesions [1, 2]. The diagnosis required repeated biopsy and immunohistochemical confirmation of BRAF V600E, which had direct therapeutic implications [1, 2].

**2) CNH is a rare but relevant complication**

Central neurogenic hyperventilation is classically linked to lesions of the brainstem and periaqueductal structures [3, 4], in this case, the extensive brainstem infiltration created a compelling anatomical substrate for CNH. The acid-base disturbance—concurrent respiratory alkalosis with metabolic acidosis and hyperlactatemia—supports a central mechanism compounded by local and systemic metabolic perturbations [6,7,8].

**3) Structural plus metabolic pathogenesis — a plausible dual mechanism**

Beyond direct disruption of respiratory centres, molecular oncogenic effects may have contributed. BRAF V600E activates downstream MAPK and PI3K/AKT/mTOR signalling, pathways that promote aerobic glycolysis (the Warburg effect) [1]. Enhanced glycolytic flux raises lactate production and can acidify the local microenvironment; local pH/lactate changes may stimulate central chemoreceptors and exacerbate hyperventilation [4,6,7]. While causality cannot be proven from a single case, this structural–metabolic hypothesis provides a coherent mechanistic framework consistent with the biochemical and radiological data[6, 7, 8].

**4) Objective metabolic response to BRAF inhibition with persistent functional impairment**

The PET-CT at ~1 year after starting vemurafenib showed resolution of intracerebral hypermetabolic foci and reduced spinal cord metabolic activity—objective evidence of biological response to targeted therapy [1,2]. This aligns with published reports

showing radiological and clinical benefit of BRAF/MEK inhibitors in ECD, including CNS disease [1,2]. However, the patient's functional recovery remained limited, likely reflecting a combination of irreversible structural injury, suboptimal rehabilitation engagement, and fluctuating adherence to supportive care and medication logistics. This dissociation between imaging response and functional outcome emphasises that targeted oncologic therapy, while often necessary and effective for disease control, must be integrated with robust rehabilitation and psychosocial support to maximise patient-centred outcomes[1].

**5) Practical implications for management and follow-up**

Early molecular testing (BRAF V600E) should be prioritised in suspected CNS histiocytosis because confirmation opens the door to rapid targeted therapy that can reverse metabolic activity and possibly limit further neurological deterioration [1,2]. Perioperative recognition of CNH is crucial because respiratory management differs from standard pulmonary causes of tachypnoea

[4,7]. Multidisciplinary co-ordination (neurology, neuro-intensive care, neurosurgery, oncology, rehabilitation and dermatology) is essential for optimal results [1]. Access and continuity of drug supply, dermatologic monitoring for BRAF inhibitor adverse effects [1], and structured rehabilitation programmes are practical determinants of long-term outcome [8].

Limitations. This is a single-patient report; mechanistic inferences remain hypothetical. Longitudinal functional outcome and formal neuropsychological/functional assessments would strengthen interpretation but were not available at the time of this report. Follow-up is ongoing.

## 9. Conclusion

We report a rare case of CNS-limited BRAF V600E–mutated Erdheim–Chester disease complicated by central neurogenic hyperventilation. The case highlights diagnostic pitfalls of infiltrative brainstem lesions, provides a plausible structural–metabolic explanation for CNH, and documents metabolic response to vemurafenib. The clinical course underscores the need for early molecular diagnosis, prompt targeted therapy, and sustained multidisciplinary rehabilitation to improve functional outcomes.

## 10. Patient Perspective

The patient provided informed consent for publication and expressed relief at having a molecular diagnosis and receiving targeted therapy. He emphasised difficulties with access to medication and the need for continued rehabilitation and dermatologic support.

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